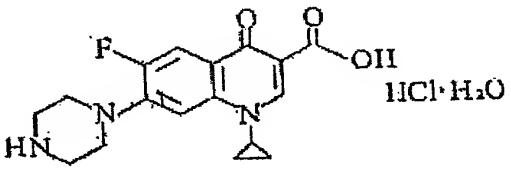
CIPROFLOXACIN HCl

This invention relates to Ciprofloxacin Hydrochloride-containing compositions, useful for the treatment of diseases.

The main composition is Ciprofloxacin Hydrochloride and the chemical name in accordance with the Merck Index II[th] Edition, page 360 (1989) has the International Non-propriety Name (INN) for I-cyclopropyl- 6-fluoro-1 ,4-dihydro-4-oxo- 7-(I-piperazinyl)-3-quinolinecarboxylic acid of the structural formula:



$C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

disclosed, together with the process for the preparation thereof, in U.S. Patent No. 4,670,444. Ciprofloxacin is a broad-spectrum antibacterial active principle.

The Ciprofloxacin Hydrochloride may easily be obtained on the market place or may be prepared by any of the methods disclosed in Spanish Patents Es-2006099 and ES-2006098.

Ciprofloxacin Hydrochloride is a white or off-white powder, which is odorless and has a bitter taste with a wide range antibacterial activity against Excherichia Coli, Klebsiella SPP., and other Enterobacter SPP., Bacillus – negative. The antibacterial action against Pseudomonas aerugenosa, golden yellow Staphylococcus and Streptococcus pneumoniae is better than other known derivatives i.e. Norfloxacin and Peifloxacin but the antibacterial action against Streptococcus SPP. Is less than Penicillin kinds of antibiotic.

The antibacterial action results from the inhibition of bacterial DNA gyrase for combating various types of disorders. Ciprofloxacin Hydrochloride may be used in combination with an amino glycoside or with beta-lactam antibiotics.

The present inventor is aware of the existence of prior art describing ciprofloxacin pharmaceutical preparations which may be used for combating diseases whereby, in view of the high efficacy and broad spectrum of this antibacterial active principle, there is a felt the desirability of developing new compositions containing it, suitable for such application.

The invention seeks to provide aqueous ciprofloxacin compositions suitable for use in the treatment of the following infections caused by sensitive bacteria:

1. Upper respiratory tract infections including tonsillitis, sinusitis, otitis media and pharynx inflammation.

2. Lower respiratory tract infections including acute and chronic bronchitis, bronchiectasis and pneumonia.

3. Urinary tract infections including urethritis, cystitis, pyelonephritis, prostatitis and pelvic inflammatory.

4. Gastro-intestinal infections including enteric fever and infective diarrhea.

5. Skin and soft tissue infections.

6. Wounds infections.

7. Infections caused by other sensitive bacteria.

This objective is achieved by composition according to the present invention characterized in that they comprise the following essential components, in the amounts given hereinafter.

i. 300 g of Ciprofloxacin;

ii. 65 g of starch;

iii. 18 g of Carboxymethyl starch Sodium;

iv. 4 g of Magnesium Stearate

The technical specifications of the component of the present invention are as follows:

2.1 Technical specifications of Ciprofloxacin Hydrochloride

Items	Specifications
1. Identification	
A. IR Test	Conform
B. TLC Test	Conform
C. Chloride Test	Conform
2. pH	3.0 ~ 4.5
3. Water	4.7 ~ 6.7%
4. Residue of ignition	□ 0.1%
5. Sulfate	□ 0.04%
6. Heavy metals	□ 0.002%
7. Limit of fluoroquin-olonic acid	□ 0.2%
8. Chromatographic purity Single impurity: Total impurities:	 □ 0.2% □ 0.5%
9. Assay	98.0 ~ 102.0%

2.2 Technical specifications of Magnesium Stearate

Items	Specifications
1. Identification	
A. Magnesium test	Conform
B. The retention time test	Conform
2. Microbial limits	
A. The total aerobic and microbial count	□ 1000 per g
B. The total combined molds and yeast count	□ 500 per g
C. Salmonella and Escherichia coli	Absence
3. Acidity or alkalinity	□ 0.05 ml of 0.1 N HCL
4. Loss of drying	□ 6.0%
5. Specific surface area	0.05 ~ 0.15
6. Limit of chloride	□ 0.1%
7. Limit of sulfate	□ 1.0%
8. Lead	□ 0.001%
9. Relative content of stearic Acid and palmitic acid	Meet the requirements of USP24
10. Assay	4.0 ~ 5.0% Mg (dried basis)

2.3 Technical specifications of starch

Items	Specifications
1. Identification	
A. Solubility	A translucent, whitish jelly
B. Color test	Reddish violet to deep blue
2. Microbial limits	
Salmonella species and Escherichia coli	Absence
3. pH	4.5 ~ 7.0 for Corn starch, Tapioca starch and wheat Starch; 5.0 ~ 8.0 for Potato starch
4. Loss of drying	□14.0%
5. Residue on ignition	□ 0.5%
6. Iron	□ 0.002%
7. Oxidizing substances	□ 0.002%
8. Sulfur dioxide	□ 0.008%

2.4 Technical specification of Carboxymethylstach Sodium

Items	Specifications
1. Identification	
A. Color test	Add iodine indicator, produce blue
B. Sodium sact test	Conform
Acidity and alkalinity	5.5 ~ 7.5
Total chlorine content	□ 3.5% (dried basis)
Loss of drying	□ 10.0%
Iron	□ 0.004%
Heavy metals	□ 0.002%
Assay	Contain Sodium 2.0 ~ 4.0% (Calculated on dried basis)

The daily dose of the composition of the present invention can vary over broad limits depending on several factors, e.g. on the activity of the active ingredients, the patient's condition and age, the severity of the disease.

The oral dose as a rule: usual dose; single dose is 200-250mg; severe symptom; single dose is 400-500mg, twice a day taken with boiled water. It has

to be stressed that these doses figures are intended for information only, and administered dose must be determined each time by the physician therapeutist.

When healthy adults take orally 200mg, 1.5-2 hours later the peak concentration will reach 1.21 +- 0.03 ug/ml; if take orally, 1.5-2 hours later the peak concentration will reach 2.73 +- 0.43 ug/ml. The half-life is four hours ($t_{1/2}$=4h). In the majority of indications twice dosage may be taken orally. The product distribute mainly in bile, mucus, saliva, bone and prostate gland but the concentration is lower in brain tissue. It may be metabolized partly in liver and pharmaceutical concentration in urine may be retainable.

According to the further aspect of the present invention there is provided a process appropriate for preparing the compositions of the invention comprising the following steps:

i. Mixing the appropriate prescription amount of Ciprofloxacin Hydrochloride, Starch and Carboxymethyl starch into a container;
ii. Adding some amount of starch thick liquid and stir until a soft material formed in the previous step and then dry it at a temperature preferably 70 C for 4 hours;
iii. Granulating the soft material formed in the previous step and then dry it at a temperature preferably 70 C for 4 hours;
iv. Take it out and arrange the grain;

v. Adding some amount of Magnesium Stearate in order to fill well in a capsule using an automatic filling machine;

According to a preferred feature, the capsules are packaged in a blister foil. It does obtained compositions, which have excellent properties with regard to physical and microbial stability, without the need to use preservatives and are particularly appropriate for oral administration.

The following example is given for a better understanding of this description, without being deemed to be a limitation of the scope of the present invention.

EXAMPLE I

Weight 200 kg of Ciprofloxacin Hydrochloride, 37.73 kg of starch and 12.00 kg of Carboxymethyl starch sodium into a container, mix well. Using 5.60 kg of starch and 80 kg of water prepare starch thick liquid (7%). Then add these liquids to the container until soft material is obtained. The total quantity of starch is 43.33 kg. After drying and arranging grains add 2.76kg of Magnesium Stearate in order to fill well.

Through drying about 80kg of water may be lost, but no ingredients may be removed and overage. Before filling capsules, the tester must sample and test. According to the test result adjust quantity of each capsule.

The technical specification of the present composition is shown by the following:

Items	Specifications
Identification A. The retention time test B. TLC test	The retention time of sample corresponds to that of the standard. The result obtained from test solution corresponds to that of Standard Solution
Dissolution of dosage units	Not less than 80% Uniformity Meet the requirements
Assay	90.0 ~ 110.0%

Details of the assay and other test procedure for finished product including data analysis:

[Identification]

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the standard preparation obtained as directed in the Assay.

B: Place a number of capsules, equivalent to about 1500 mg of Ciprofloxacin, in a suitable flask containing about 750mL of water, and sonicate for about 20 minutes. Dilute with water to 1000mL, add mix. Centrifuge a portion of this suspension, and use the clear supernatant solution obtained as the test solution. Dissolve a quantity of USP Ciprofloxacin Hydrochloride RS in water to obtain a standard solution containing 1.5mg per mL. Proceed as directed for Identification test B under Ciprofloxacin Hydrochloride. Starting with Separately apply, as 1-cm bands, 5 uL each. "Except to use 10 uL each of the test solution and the standard solution: the specified result is obtained.

[Dissolution]

Medium : Water 900 mL

Apparatus: 50 rpm

Time: 30 minutes

Procedure – Determine the amount of Ciprofloxacin Hydrochloride ($C_{17}H_{18}FN_3O_3$.HCl) dissolved from ultraviolet absorbance at the wavelength of

absorbance at about 276 nm of filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a standard solution having a known concentration of USP Ciprofloxacin Hydrochloride RS in the same medium.

Tolerances - An amount of $C_{17}H_{18}FN_3O_3$. HCI equivalent to not less than 80% (Q) of the labeled amount of Ciprofloxacin $C_{17}H_{18}FN_3O_3$ is dissolved in 30 minutes.

Calculated formula:

$$Q = \frac{A_T X 900}{A_S X\ LX\ D_S} \times 100\%$$

A_T - Absorbance obtained from test Solution

A_S - Absorbance obtained from Standard Solution

D_S - Diluted multiple of Standard solution

L - Labeled quantity

Uniformity of dosage units:

Take 20 pills Ciprofloxacin Hydrochloride capsules, weigh their internal drug, and the weight discrepancy is ±7.5%.

[Assay]

Mobile phase, Resolution solution and Chromatographic system – prepare as directed in the Assay under Ciprofloxacin Hydrochloride.

Standard preparation – Dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS quantitatively in water to obtain a solution having a known concentration of about 0.3 mg per mL.

Assay preparation – Transfer 5 capsules to a 500-mL volumetric flask, add about 400 mL of water, and sonicate for about 20 minutes. Dilute with water to volume, and mix. Dilute an accurately measured volume of this solution quantitatively with water to obtain containing the equivalent of about 0.25 mg of Ciprofloxacin per mL.

Procedure – proceed as directed for Procedure in the Assay under Ciprofloxacin Hydrochloride. Calculate the quantity in mg of Ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in each capsule taken by the formula:

$$(331.35/367.81)\,(CL / D)\,(rL / rs)$$

In which 331.35 and 3 7.81 are the molecular weights of Ciprofloxacin and anhydrous Ciprofloxacin Hydrochloride, respectively, C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the Standard preparation, calculated on the anhydrous basis. L is the labeled quantity, in mg per mL of Ciprofloxacin in the Assay preparation, based on the labeled quantity per capsule and the extend of dilution, and rL and rs are the ciprofloxacin peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Detailed report of stability studies to justify shell life (accelerated or long terms).

1. **Long term testing**

1.1 Scope

Three batches (980 01, 980 02, 980 03) of Ciprofloxacin Hydrochloride capsules have been subjected to stability tests under 20°C±2°C and 0% RH ± 5%. So far, two year' stability results are available.

1.2 Packaging

The container to be used is the same as the actual packaging used for storage and distribution.

1.3 Storage condition

Temperature and humidity is 25°C±2°C and 0% RH ±5%.

2. Accelerated Testing

2.1 Scope

Our factory has performed a new stability program according to the "Stability testing guideline for medicinal products in European Union".

2.2 Packaging

The container to be used in the same as the actual packaging used for storage and distribution.

2.3 Storage condition

Under 40°C±2°C and 75% RH ±5% for 6 months.

3. Analytical Items

The following items were carried out in order to determine any changes in this product.

3.1. Appearance.

3.2. Dissolution.

3.3. Uniformity of dosage units.

3.4. Assay.

Item 3.1 was tested by estimation, items 3.2, 3.3, 3.4 were tested in accordance with section 7 "Test procedure for finished products".

4. Results

Please see table I, II, III, IV.

5. Conclusion

In well-closed containers, no significant change was observed up on storage at 25°C ± 2°C and 60% RH ± 5% for two years. In no case degradation products were observed. We will continue long term testing in order to confirm the final validity of this product, but it should be up to two years.

Table I

Long term testing results of Ciprofloxacin Hydrochloride capsules Batch No.: 980601

Items Month	Appearanced	Uniformity of dosage units	Dissolution	Assay
0	Off-white particle	Conform	94%	98.4%
3	No change	Conform	93.5%	98.0%
6	No change	Conform	93.2%	98.1%
9	No change	Conform	93.0%	97.6%
12	No change	Conform	93.3%	97.5%
18	No change	Conform	92.5%	96.8%
24	No change	Conform	92.1%	97.0%

Table II

Long term testing results of Ciprofloxacin Hydrochloride capsules Batch No.: 980602

Items Month	Appearanced	Uniformity of dosage units	Dissolution	Assay
0	Off-white particle	Conform	94.2%	97.5%
3	No change	Conform	94.0%	97.2%
6	No change	Conform	94.1%	97.3%
9	No change	Conform	93.8%	97.0%
12	No change	Conform	93.6%	96.9%
18	No change	Conform	93.3%	96.5%
24	No change	Conform	93.2%	96.6%

Table III

Long term testing results of Ciprofloxacin Hydrochloride capsules Batch No.: 980603

Items Month	Appearanced	Uniformity of dosage units	Dissolution	Assay
0	Off-white particle	Conform	93.8%	98.0%
3	No change	Conform	93.5%	97.8%
6	No change	Conform	93.6%	97.6%
9	No change	Conform	93.2%	97.1%
12	No change	Conform	93.4%	97.0%
18	No change	Conform	92.9%	96.5%
24	No change	Conform	92.6%	96.3%

Table IV

Accelerated testing results of Ciprofloxacin Hydrochloride capsules Batch No. : 980601; 980602; 980603

Appearance of capsules: Off-white particle in hard capsule.

Storage Time	Batch No.	Apperance	Uniformity of Dosage units	Dissolution	Assay
Initial (15/06,1998)	980601	Conform	Conform	94.0%	98.4%
	980602	Conform	Conform	94.2%	97.5%
	980603	Conform	Conform	93.8%	98.0%
I month	980601	No change	Conform	94.1%	97.9%
	980602	No change	Conform	94.0%	97.2%
	980603	No change	Conform	93.6%	97.5%
2 month	980601	No change	Conform	93.7%	97.4%
	980602	No change	Conform	93.9%	96.8%
	980603	No change	Conform	93.6%	96.9%
3 month	980601	No change	Conform	93.5%	96.6%
	980602	No change	Conform	93.4%	96.1%
	980603	No change	Conform	93.5%	96.2%
6 month	980601	No change	Conform	93.0%	96.0%
	980602	No change	Conform	92.7%	95.4%
	980603	No change	Conform	92.8%	95.0%